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DATE MAILED: 02/09/90

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☐ This application has been examined ☒ Responsive to communication filed on 10-30-89 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ___ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-21 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 1-21 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).

12. ☐ Acknowledgement is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.

13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

The drawings objection in the Office action of April 27, 1989 is repeated.

Claims 1-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 14 are vague and confusing. In step (a) as presently claimed, at least some, if not all, of the "plurality of denatured pairs" can be identical. If so, a utility problem can exist, but for the sake of brevity a utility rejection has not been made. There is no requirement that each or any pair be different. That is, there is no requirement that the amplification probes differ. This becomes important at step (b) since there is no requirement for hybridization at different loci of the template so contiguous hybridization need not occur. Step (e) is unclear since the only apparent outcomes after one cycle are either the original starting materials (if amplification probes are not contiguous) or ligated amplification probes. That is, self-annealing occurs at step (b) and ligation occurs at step (c) which uses the amplification probes of step (a). Thus, amplification does not appear to occur. For claims 1, 14, 19 and 21 the use of "same" in the claim language "same hybridizing member" is still unclear since the adjective appears to be surplusage and probably can be eliminated without altering the scope of the claims.

Claims 6 and 14 are vague and confusing. At claim 6 (c) and 14 (h), there is no clear delineation of hybridized label from unhybridized label. In other words, the amplification product is not definitively detectable. In addition, even if the hybridized form is uniquely detectable, there is no apparent utility in having unlabeled detection probes present since the detection is for the label which is unaffected by the presence or absence of unlabeled detection probes. Finally, in claim 6 (a) and (b) or 14 (f) and (g), it is unclear if each detection probe must be complementary to portions of two ligated amplification probe segments, or the detection probes can be shorter than the nucleic acid segments but be contiguous at the same juncture as the ligated amplification probe segments. The present claim language allows hybridization to 2 amplification probe segments so the necessity of 3 such probe segments is unclear.

Claims 7, 9 and 15 are vague and confusing since it is unclear when the steps are performed. Claims 8 and 13 are confusing with "the other" detection probe since more than 2 such probes are present in the parent claim. Claims 19 and 21 are vague since they are to reagents but refer to a "reaction" in "drive the reaction forward" without a clear statement of what the reaction

is. Without this knowledge, it is difficult to know an excess of reactant exists. Claim 20 is still confusing since it is unclear if each detection probe must be complementary to portions of two ligated amplification probe segments or the detection probes can be shorter than the amplification probe segments but be contiguous at the same juncture as the ligated amplification probe segments. Again, the necessity of 3 amplification probe segments is unclear. Claim 21 is further vague since there is no requirement for the amplification member probe pairs to differ from each other. It is unclear if these probe sequences can be identical or if they differ.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 19-21 are rejected under 35 U.S.C. 103 as being unpatentable over Whiteley et al (EPO).

Whiteley et al (EPO) uses two hybridization probes in a hybridization assay for a specific nucleic acid sequence. The two probes have nucleic acid sequences such that they can hybridize contiguous to each other when the target sequence complementary to both probes is present. Following hybridization, the contiguous probes are ligated by an enzyme or other chemical process, the ligated probes are denaturedly separated from the target strand, and after electrophoretic separation the ligated nucleic acid sequence is detected by a label that was attached to one of the probes. The unlabeled probe can have a reagent attached to it that can specifically react with an immobilized complementary reagent to allow label detection on a solid support when ligation has occurred. Kits with the appropriate reagents are also shown by Whiteley et al. It would have been obvious to provide the probes of Whiteley et al as pairs of complementary nucleic acid sequences because the probes were synthesized as the complementary strands of the target sequence, so it would have been a routine procedure to synthesize complementary strands of the originally synthesized probes.

Claims 1-5 are rejected under 35 U.S.C. 103 as being unpatentable over Whiteley et al in view of Mullis et al. Mullis et al shows an amplification procedure for detecting a specific nucleic nucleic acid sequence where two probes that specifically hybridize with sequences on opposite sides of the complementary strands that include the target nucleic acid sequence. Following hybridization of these probes, extension from the probes through the target sequence and the probe sequence on the opposite side is accomplished, the complementary strands are separated for use as templates for another cycle of probe hybridization, extension, and strand separation. At least at the final cycle, labeled nucleotides are added for incorporation into the extension product for subsequent detection purposes. It would have been obvious to perform the procedure of

Whiteley et al through several cycles in order to amplify the target sequence present in a sample in view of Mullis et al since both references are to detection of a target nucleic acid sequence through a hybridization procedure. It would have been obvious to include more probes in the Whitely-Mullis procedure for the expected lower probability of unspecific probe hybridization as Whiteley et al disclose.

Claims 6-13 are rejected under 35 U.S.C. 103 as being unpatentable over Whiteley et al in view of Palva et al.

Palva et al shows hybridization assays for a target nucleic acid sequence where different labeled and unlabeled subsequences are ligated together. The labeled probes can be constructed so they are contiguous and hybridize to the target sequence. It would have been obvious to use the technique of Whiteley et al to detect ligated nucleic acid sequences in view of Palva et al, i.e. the probes of Whitely et al to detect the ligated sequences of Palva et al in hybridization procedures. It would have been obvious to use proximity labels in the Whiteley-Palva procedure for the expected enhanced or unique signal generated when the reactive components combine in the hybridization process.

Claims 14-18 are rejected under 35 U.S.C. 103 as being unpatentable over Whiteley et al in view of both Mullis et al and Palva et al.

It would have been obvious to sequentially perform the Whiteley-Mullis and Whiteley-Palva hybridization procedures for the expected amplification, as Mullis et al shows, and specificity, as Whiteley et al and Palva et al shows, the combination would provide.

Applicants' arguments filed October 30, 1989 have been fully considered but they are not deemed to be convincing of patentability. The synthesis of complementary strands is not always necessary, but when such synthesis is required, the reference directs a person to its accomplishment. Mullis et al shows nucleic acid sequence amplification by hybridization and elongation from a given probe, denaturation, rehybridization of probes to complementary strands, elongation from these probes, denaturation, etc., ie amplification of a given template nucleic acid sequence. Whiteley et al shows probe hybridization, elongation by hybridizing contiguous probes, ligation, and denaturation. Thus Mullis et al shows amplification following single probe hybridization and Whiteley et al show double probe hybridization and ligation. Both references are directed toward detection of target nucleic acid sequences. Palva et al shows detection of nucleic acid sequences with probe nucleic acid fragments that can be joined (see Figure 5b or 5c) with the use of a ligase (see column 9, line 52 to column 10, line 14).

Applicant's amendment necessitated the new grounds of rejection. Accordingly, THIS ACTION IS MADE FINAL. See MPEP 706.07(a). Applicant is reminded of the extension of time policy set forth in 37 CFR 1.136(a). The practice of automatically extending the shortened statutory period an additional month upon the filing of a timely first response to a final rejection has been discontinued by the Office. See 1021 TMOG 35.

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE (3) MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO (2) MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE (3) MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 CFR 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX (6) MONTHS FROM THE DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication should be directed to Richard Wagner at telephone number 703-557-3434.

RW

Wagner:st

1/18/90

Esther M. Kepplinger

ESTHER M. KEPPLINGER
PRIMARY EXAMINER
ART UNIT 182